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Relapse of Precursor B-Cell Acute Lymphoblastic Leukemia as an Isolated Central Nervous System Mass Lesion 9 Years After Initial Diagnosis

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Seven years after completion of chemotherapy for acute lymphoblastic leukemia, diagnosed at the age of 5 years, a black female presented with signs of increased intracranial pressure. Neuroimaging showed a large enhancing extra-axial occipital tumor mass. The resection specimen showed morphologic, cytogenetic, and immunophenotypic features consistent with relapse of the primary leukemia. Bone marrow examination was negative for malignancy. The long duration of complete remission followed by the formation of a mass in the central nervous system are highly unusual features of recurrent acute lymphoblastic leukemia.

Key words: acute lymphoblastic leukemia, central nervous system, relapse, mass lesion, CT, MRI

INTRODUCTION

Children with acute lymphoblastic leukemia (ALL) who have maintained a complete remission (CR) for >5 years following the completion of therapy will rarely relapse. Most late relapses occur in the bone marrow [1–8], but occasional cases involve extramedullary sites [9–13]. Central nervous system (CNS) relapse may be heralded by evidence of increased intracranial pressure or focal neurological deficits, but is currently most often detected in asymptomatic patients with malignant cells in cerebrospinal fluid samples obtained while patients are still receiving therapy [14–17].

Intracranial mass lesions develop in ~1:400–1:600 ALL patients [18,19]. However, most of these masses are found to be glial neoplasms and as such represent the most common type of solid second malignancy in treated leukemics. With rare exceptions, these secondary gliomas have been reported in patients who received craniospinal radiation in order to prevent CNS relapse of their leukemia [20,21].

We present a case of a 14-year-old female treated exclusively with chemotherapy for acute lymphoblastic leukemia, FAB L1, diagnosed at age 5, who developed papilledema 9 years later due to an occipital mass. Although a secondary brain tumor might have been more likely in this setting, the morphologic, immunophenotypic, and cytogenetic features were consistent with the original leukemia.

CASE REPORT

A 5-year-old black female presented with atraumatic left elbow pain, weakness, decreased activity, fever, rhinorrhea, and anorexia. Physical examination revealed pallor, minimal splenomegaly, and cervical and inguinal lymphadenopathy. A CBC revealed 13 K/cmm WBC with 88% blasts, anemia (Hgb 3.6 g/dl), and thrombocytopenia (35 K/cmm). Bone marrow aspiration confirmed a diagnosis of acute lymphoblastic leukemia (ALL), FAB L1. No malignant cells were observed in cerebrospinal fluid. She was enrolled in Pediatric Oncology Group (POG) Protocol #8036 [22], receiving vincristine, prednisone, L-asparaginase, cyclophosphamide, methotrexate, and 6-mercaptopurine for systemic control, and triple intrathecal therapy consisting of cytarabine, hydrocortisone, and methotrexate for CNS prophylaxis. She achieved a complete remission (CR) 1 month following

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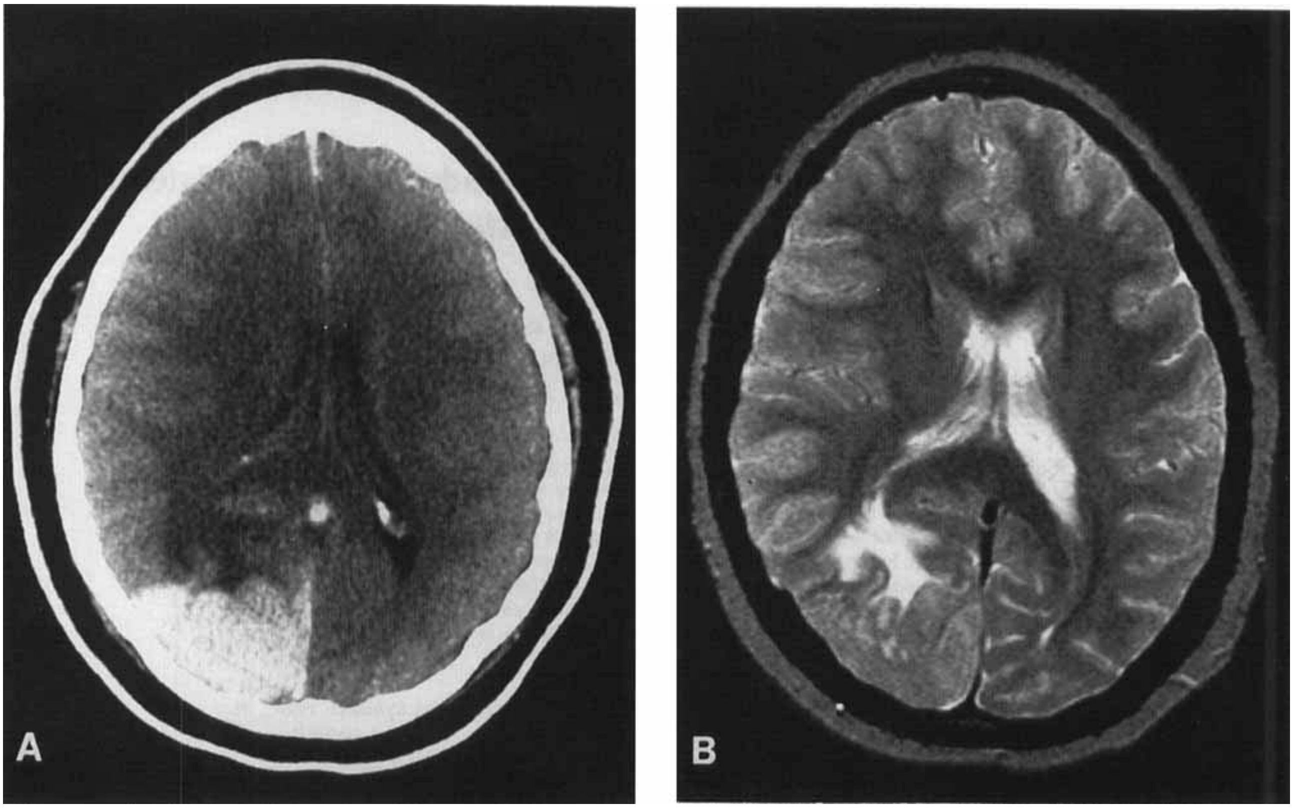

Fig. 1. Neuroimaging findings of recurrent isolated CNS leukemia. **A.** Post-contrast CT shows intense, homogeneous enhancement within the tumor. **B.** Axial T_2 image shows increased signal intensity in edematous white matter. The tumor mass remains of relatively low signal intensity due to hypercellularity.

diagnosis and completed therapy in CR 23 months after diagnosis.

Seven years after completion of therapy, she complained of blurred vision, headache, and persistent recurrent vomiting. Examination revealed an obese girl with severe papilledema, but no other neurological signs, organomegaly, or lymphadenopathy. CBC revealed a mild increase in the percentage of mature lymphocytes (49%, WBC count 8.5 K/cmm), and a normal hematocrit (41%) and platelet count (187 K/cmm). Neuroimaging studies revealed a 5 × 6 cm extra-axial tumor in the right occipital region. The relatively high density of the tumor mass by computed tomography (CT) and the low T_2 signal on magnetic resonance imaging (MRI) suggested a hypercellular lesion (Fig. 1). Because of the papilledema, preoperative lumbar puncture was deferred, and steroid therapy was initiated.

At craniotomy, a large amount of pale, soft, rubbery tissue herniated through the dural incision. Around the circumference of the mass, there were no identifiable tissue planes. Tumor extended along the midline overlying the cortex and over the falx and tentorium. An estimated 95–98% of the tumor was removed.

Tumor morphology was consistent with a malignant lymphoblastic infiltrate. Chest X-ray, abdominal CT scan, and bone scan were negative. Bone marrow aspirate smear, clot section, and trephine biopsy revealed a mildly hypercellular marrow with myeloid hyperplasia and no evidence of leukemia. Postoperative lumbar puncture revealed no malignant cells. However, the bone marrow and lumbar puncture were performed following the 5-day course of steroid administration for increased intracranial pressure.

Following surgery, the patient did well, with complete resolution of visual disturbance. She is currently doing well with no evidence of recurrence. She is being treated as per POG protocol 9061 [23] for isolated CNS relapse.

Pathologic Findings

The initial bone marrow aspirate obtained 9 years prior to relapse consisted of 80% lymphoblasts, 95% of which had L1 morphology (Fig. 2A) and 70% of which exhibited coarse block positivity with the periodic acid Schiff reaction. Leukocyte acid phosphatase, α-naphthyl butyrate esterase, naphthol ASD chloroacetate esterase, and myeloperoxidase were negative. Blasts were also positive for terminal deoxynucleotide transferase (TdT) by immunofluorescence, and were E-rosette negative. Flow cytometry performed at Duke University Medical Center (Durham, NC) revealed positive staining of 90% of tumor cells for HLA-DR and CD24. There was partial (20–30% of cells) positivity for CD20. Immunoglobulin

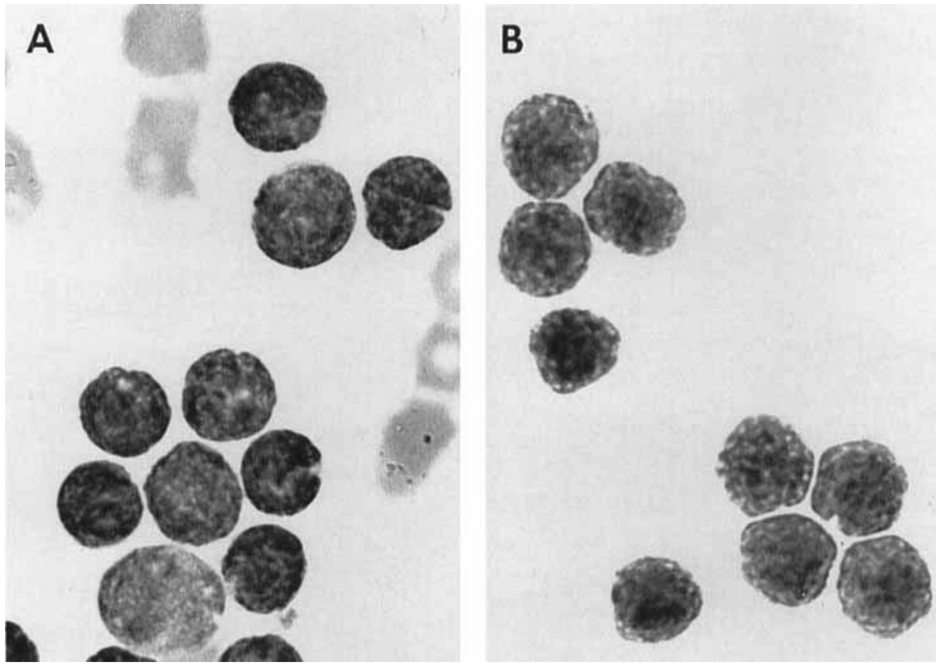

Fig. 2. Cytology of lymphoblasts in original leukemia and CNS relapse. **A.** Bone marrow aspirate smear at age 5 with predominance of L1 lymphoblasts. **B.** Touch preparation of occipital brain lesion at age 14 reveals L1 lymphoblasts with morphology similar to the bone marrow infiltrate of 9 years earlier. Air-dried, Wright stain (×14,000).

analysis performed at the University of Alabama (Birmingham) was positive for cytoplasmic mu and negative for surface IgM. Cytogenetic analysis revealed that 11 of 21 cells had a hyperdiploid karyotype: 60,X, -X,+5,+5,+6,+6,+7,+8,+11,+12,+14,+15,+17,+18, +19,+21,+22.

The multiple tan-white tissue fragments received from the occipital tumor 9 years later ranged from $3.5 \times 3.0 \times 1.0$ cm to $1.4 \times 0.7 \times 0.4$ cm. Touch preparations contained L1 lymphoblasts with morphologic features similar to those in the original leukemia, although differences in preparation and staining precluded comparison of subtle features. The cells were round and discohesive with occasional folded or convoluted nuclear contours, relatively coarse chromatin, and scant cytoplasm (Fig. 2B). Histologic sections revealed sheets of discohesive small, round, fairly monomorphous cells with somewhat coarsely clumped chromatin, inconspicuous nucleoli, and scant cytoplasm. These lymphoblasts were admixed with numerous tingible-body macrophages, resulting in a "starry sky" appearance. Most sections consisted primarily of tumor with a delicate fibrovascular background in which no neuroglial elements or immunohistochemical staining for neuron-specific enolase were appreciated. In one section containing brain parenchyma, the tumor appeared confined to the meninges adjacent to uninvolved superficial cortex, whereas in another, there was minimal infiltration of lymphoblasts into brain tissue as well as cuffing of cerebral blood vessels by the malignant cells (Fig. 3). Immunophenotypic analysis revealed that the majority of tumor cells were positive for CD19, CD20, CD10, CD34, CD38, HLA-DR, and intracytoplasmic CD22 and TdT. There was dim positive staining for CD45, and absence of staining for surface light chains, T-cell and myeloid markers, and CD56. In specimens received for cytogenetic analysis, no dividing cells were found in a direct preparation or in overnight and 48-hour cultures. However, the DNA index performed at Saint Jude Children's Research Hospital (Memphis, TN) was 1.29, consistent with the 60-chromosome karyotype present at the time of original diagnosis.

DISCUSSION

Morphologic, immunophenotypic, and cytogenetic analysis of the original leukemia and the CNS lesion all suggest that this case represents a relapse of the original disease rather than a new primary CNS lymphoma. Cytologic features of the lymphoblasts in the original leukemia and CNS lesion were similar. Immunophenotypic analysis revealed a precursor B-cell phenotype *in both* specimens, although a more limited panel was employed on the initial sample. The persistence of hyperdiploidy also suggests that both tumors derive from the same clone. Although molecular methods have recently been

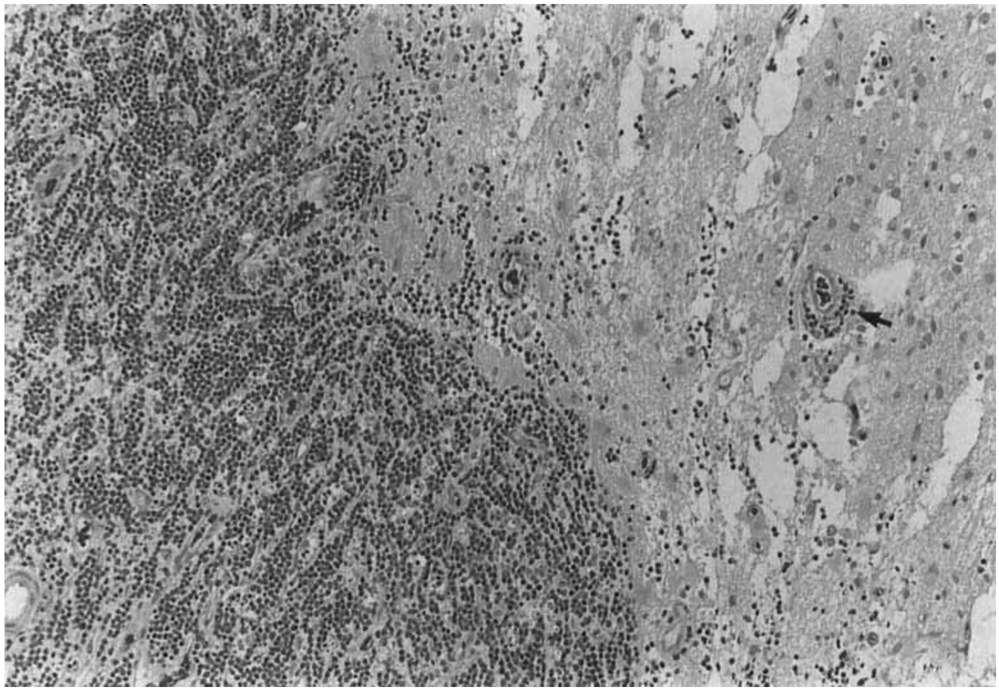

Fig. 3. Section of occipital brain reveals sheets of round, regular, evenly dispersed lymphoblasts punctuated by tingible-body macrophages, as seen in lymphoblastic lymphoma. Whereas the brain-tumor interface was well demarcated in some areas, there was focal infiltration of brain parenchyma by lymphoblasts as well as perivascular cuffing by malignant cells (arrow) in this region. Formalin fixation, Hematoxylin and eosin stain (×1300).

implemented in similar cases to more definitively demonstrate clonality [7,24], unstained smears from the original leukemia were no longer available in this case.

We present this case as an isolated CNS relapse of ALL. There was a 5-day interval between the craniotomy and the lumbar puncture and bone marrow, during which intravenous and then oral steroids were administered. Although it seems unlikely, small numbers of malignant lymphoid cells may have been present in the bone marrow prior to administration of glucocorticoids.

Immunophenotype and ploidy have prognostic significance in childhood ALL. In our case, however, the original and recurrent tumor were hyperdiploid and the recurrent tumor expressed CD34, which are features generally associated with a good prognosis in childhood precursor B cell ALL [25]. Malignant cells from the CNS relapse did not express CD56, an isoform of the neural cellular adhesion molecule (NCAM). This is of interest, as NCAM has been identified in a subset of peripheral T-cell lymphomas with a predilection for the CNS, inviting speculation that it may play a role in tumor localization in some lymphoid malignancies [26].

Early successes in treatment of acute lymphoblastic leukemia were marred by CNS relapse in >50% of patients [14,27]. Despite institution of CNS prophylaxis using chemotherapy and/or radiation therapy over the past three decades, 5–10% of children in remission from ALL will suffer a CNS relapse. The vast majority of these relapses occur within 3–5 years of the first CR, often while the patient is still on maintenance chemotherapy [15,16,28–34]. Reports similar to our case in which CNS relapse occurred 9 years after initial diagnosis are exceedingly rare; one series of Scandinavian children included a relapse after 13 years CR [13].

In addition to the long duration of first CR, the clinical presentation of this case is extremely unusual. Whereas symptomatic CNS relapse as seen in the present case was relatively common in previous decades [14,15,35], the majority of cases of CNS relapse in current series involve asymptomatic patients with blasts in the cerebrospinal fluid [16,17]. This difference likely reflects more frequent use of lumbar puncture to deliver intrathecal therapy and detect malignant cells. Meningeal-based masses as seen in this patient are rare and occur most often in acute myelogenous leukemia [36]. We could find no reference to additional cases of CNS mass lesions due to relapse of ALL in the literature. This may partially reflect the fact that more advanced, symptomatic cases of CNS relapse were primarily seen in the 1970s, when many patients likely did not undergo detailed neuroimaging studies.

This case demonstrates that relapse of leukemia should

be included in the differential diagnosis of an intracranial mass lesion in patients with a previous diagnosis of ALL. The long interval between CR and relapse emphasizes the importance of long-term follow-up, even in cases with good prognostic features such as hyperdiploidy and CD34 positivity. In five of six recent series, although CNS relapse was often followed by bone marrow or additional CNS relapse, patients with a longer duration of first CR had a better prognosis [8,16,17,23,30,33]. A similar trend has been observed in a series of 17 cases of extramedullary relapse involving various anatomic sites, including several cases of ocular relapse [12]. The clinical course of patients such as ours with extremely late CNS relapse will thus be of interest.

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REFERENCES

1. Feldman F, Tan CV: Acute leukemia—relapse after prolonged remission. J Pediatr 76:926–927, 1970.
2. Land VJ, Berry DH, Herson J, Miale T, Ried H, Silva-Sosa M, Starling K: Long-term survival in childhood acute leukemia: "Late" relapses. Med Pediatr Oncol 7:19–24, 1979.
3. Carcassonne Y: Relapse after presumed cure of lymphoblastic leukaemia (let.). Lancet 2:473, 1981.
4. Madden M: Late relapse after presumed cure of acute lymphatic leukaemia (let.). Lancet 2:306, 1981.
5. Wyld PJ, Lilleyman JS: Late relapse after presumed cure of childhood lymphoblastic leukaemia (let.). Lancet 2:86, 1981.
6. Reynoso EE, Keating A, Baker MA: Acute leukemia occurring 19 years after treatment of acute lymphoblastic leukemia. Cancer 59:1963–1965, 1987.
7. Levasseur M, Maung ZT, Jackson GH, Kernahan J, Proctor SJ, Middleton PG: Relapse of acute lymphoblastic leukaemia 14 years after presentation: Use of molecular techniques to confirm true re-emergence. Br J Haem 87:437–438, 1994.
8. Chessells JM, Leiper AD, Richards SM: A second course of treatment for childhood acute lymphoblastic leukaemia: Long-term follow-up is needed to assess results. Br J Haem 86:48–54, 1994.
9. Reaman GH, Poplack DG, Pizzo PA: Late soft tissue recurrence of acute lymphoblastic leukemia in a site of antecedent trauma. J Pediatr 92:849–850, 1978.
10. Chu J-Y, O'Connor DM, Cradock TV, Gale GB: Isolated testicular relapse five years after cessation of chemotherapy for acute lymphoblastic leukemia. Clin Pediatr 21:376–377, 1982.
11. Burton GV, Weinberg JB, Borowitz MJ: Extramedullary recurrence of acute lymphoblastic leukemia 15 years after initial diagnosis. Med Pediatr Oncol 12:255–257, 1984.
12. Bunin NJ, Pui C-H, Hustu HO, Rivera GK: Unusual extramedullary relapses in children with acute lymphoblastic leukemia. J Pediatr 109:665–668, 1986.
13. Nygaard R, Moe PJ, Brincker H, Clausen N, Nyman R, Perkkio M, Eilertsen ME, Johansen OJ, Vare M, Brinch L, Siimes MA: Late relapses after treatment for acute lymphoblastic leukemia in childhood: A population-based study from the Nordic countries. Med Pediatric Oncol 17:45–47, 1989.
14. Evans AE, Gilbert ES, Zandstra R: The increasing incidence of central nervous system leukemia in children. Cancer 26:404–409, 1970.
15. Pinkerton CR, Chessells JM: Failed central nervous system prophylaxis in children with acute lymphoblastic leukaemia: Treatment and outcome. Br J Haem 57:553–561, 1984.
16. Gelber RD, Sallan SE, Cohen HJ, Donnelly M, Dalton V, Tobia F, Clavell LA, Tarbell NJ: Central nervous system treatment in childhood acute lymphoblastic leukemia: Long-term follow-up of patients diagnosed between 1973 and 1985. Cancer 72:261–270, 1993.
17. Winick NJ, Smith SD, Shuster J, Lauer S, Wharam MD, Land V, Buchanan G, Rivera G: Treatment of CNS relapse in children with acute lymphoblastic leukemia: A pediatric oncology group study. J Clin Oncol 11:271–278, 1993.
18. Regelson W, Bross IDJ, Hananian J, Nigogosyan G: Incidence of second primary tumors in children with cancer and leukemia. Cancer 18:58–72, 1965.
19. Tefft M, Vawter GF, Mitus A: Secondary primary neoplasms in children. Am J Roentgen 103:800–822, 1968.
20. Rimm IJ, Li FC, Tarbell NJ, Winston KR, Sallan SE: Brain tumors after cranial irradiation for childhood acute lymphoblastic leukemia. Cancer 59:1506–1508, 1987.
21. Neglia JP, Meadows AT, Robison LL, Kim TH, Newton WA, Ruymann FB, Sather HN, Hammond GD: Second neoplasms after acute lymphoblastic leukemia in childhood. N Eng J Med 325: 1330–1336, 1991.
22. Crist W, Boyett J, Jackson J, Vietti T, Borowitz M, Chauvenet A, Winick N, Ragab A, Mahoney D, Head D, Iyer R, Wagner H, Pullen J: Prognostic importance of the pre-B-cell immunophenotype and other presenting features in B-lineage childhood acute lymphoblastic leukemia: A Pediatric Oncology Group study. Blood 74:1252–1259, 1989.
23. Ritchey AK, Pollock BH, Lauer S, Homans A, Newman E, Andejeski Y, Moore K: Delayed craniospinal irradiation (CS RT) with intensified chemotherapy for isolated meningeal relapse of childhood acute lymphoblastic leukemia (ALL) (abstr). Blood 82 (Suppl.):195a, 1993.
24. Goulden N, Langlands K, Steward C, Katz F, Potter M, Chessells J, Oakhill A: PCR assessment of bone marrow status in 'isolated' extramedullary relapse of childhood B-precursor acute lymphoblastic leukaemia. Br J Haem 87:282–285, 1994.
25. Pui C-H, Behm FG, Crist WM: Clinical and biologic relevance of immunologic marker studies in childhood acute lymphoblastic leukemia.Blood 82:343–362, 1993.
26. Kern WF, Spier CM, Hanneman EH, Miller TP, Matzner M, Grogan TM: Neural cell adhesion molecule-positive peripheral T-cell lymphoma: A rare variant with a propensity for unusual sites of involvement. Blood 79:2432–2437, 1992.
27. Hustu HO, Aur RJA: Extramedullary leukaemia. Clin Haematol 7:313–337, 1978.
28. Wells RJ, Weetman RM, Baehner RL: The impact of isolated central nervous system relapse following initial complete remission in childhood acute lymphocytic leukemia. J Pediatr 97:429–432, 1980.
29. Steinherz P, Jereb B, Galicich J: Therapy of CNS leukemia with intraventricular chemotherapy and low-dose neuraxis radiotherapy. J Clin Oncol 3:1217–1226, 1985.
30. Ortega JA, Nesbit ME, Sather HN, Robison LL, D'Angio GJ, Hammond GD: Long-term evaluation of a CNS prophylaxis trial-treatment comparisons and outcome after CNS relapse in childhood ALL: A report from the Childrens Cancer Study Group. J Clin Oncol 5:1646–1654, 1987.
31. George SL, Ochs JJ, Mauer AM, Simone JV: The importance of

an isolated central nervous system relapse in children with acute lymphoblastic leukemia. J Clin Oncol 3:776–781, 1985.
32. Kim TH, Ramsay NK, Steeves RA, Nesbit ME: Intermittent central nervous system irradiation and intrathecal chemotherapy for central nervous system leukemia in children. Int J Radiation Oncol Biol Phys 13:1451–1455, 1987.
33. Behrendt H, van Leeuwen EF, Schuwirth C, Verkes RJ, Hermans J, van der Does-van der Berg A, van Wering ER: The significance of an isolated central nervous system relapse, occurring as first relapse in children with acute lymphoblastic leukemia. Cancer 63:2066–2072, 1989.
34. Mandell LR, Steinherz P, Fuks Z: Delayed central nervous system (CNS) radiation in childhood CNS acute lymphoblastic leukemia: Results of a pilot trial. Cancer 66:447–450, 1990.
35. Willoughby MLN: Treatment of overt meningeal leukaemia in chidren: Results of second MRC meningeal leukaemia trial. Br Med J 1:864–867, 1976.
36. Barnes PD, Kupsky WJ, Strand RD: Cranial and intracranial tumors. Metastatic tumors: leukemia. In Wolpert SM, Barnes PD (eds): "MRI in Pediatric Neuroradiology." St. Louis, MO: Mosby Year Book, 1992, p. 231.